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VOLUME LXXVIII

NUMBER 2

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

February, 1946

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

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BULLETIN
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This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

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SPHINGOMYELINS: THEIR ACTION ON BLOOD CELLS, PARTICULARLY LYMPHOCYTES; THEIR SHARE IN THE NUCLEINATE-LIKE ACTION OF THE ETHER-IN-SOLUBLE FRACTION OF BRAIN LIPOIDS

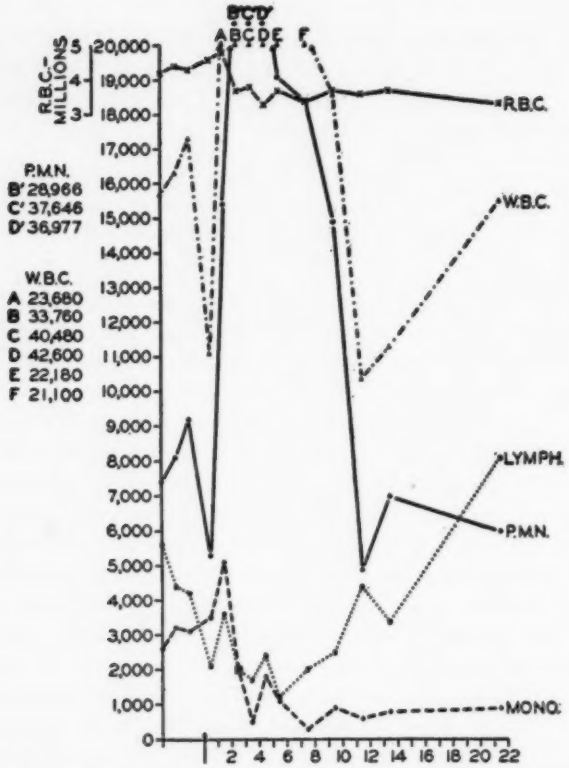
EDNA H. TOMPKINS

From the Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee, and The Laboratory of Applied Physiology, Yale University, New Haven, Connecticut

The name "protagon," which was formerly used to designate the ether-insoluble fraction of lipoids in tissues before the components of that fraction were recognized, will be employed throughout this report for the sake of brevity.

Intravenous injection of protagon obtained from beef brains has been shown to elicit a reaction of the circulating leucocytes during the following 24 hours which is similar to that obtained following intravenous injection of nucleotides (12). Chart 5 of that report has been reproduced as chart 1 of this report for purposes of reference and comparison. This reaction is characterized by leucopenia and granulopenia beginning within ½ hour of the injection; followed by lymphopenia shortly thereafter; and succeeded by considerable degrees of leucocytosis and granulocytosis beginning within 1 to 4 hours of the injection, reaching a peak 2 to 12 hours of the injection, and gradually receding to normal within 24 hours of the injection; while the lymphopenia continues for about 11 hours and is then succeeded by normal or elevated lymphocytic counts within 24 hours of the injection. The monocytes parallel the lymphocytes. Intensity of reaction and sensitivity to dosage decreased during a course of daily injections. The preparation of protagon used for these studies was shown to be free of contamination with those tissue products which might confuse the picture, i.e., acetylcholine, histamine, nucleotides. The reactions of the mononuclear cells were so reciprocal to those of the granulocytes that the possibility was considered of specific cytologic reactions to specific components of the protagon.

Protagon consists chiefly of a rather stable mixture of galactolipids and sphingomyelins (7). Protagon, obtained from the same source



In all of the charts the arrows point to the time of injection, the abscissae represent hours in relation to the time of injection, and the ordinates represent absolute numbers of blood cells. One division of the ordinate is equivalent to 1,000 white blood cells and 1,000,000 red blood cells.

CHART 1. Same as chart 5 of reference (12). It is published for the purpose of comparison with the effects obtained upon the blood cells by intravenous injections of sphingomyelins. This rabbit was given, intravenously, 59 mg. of protagon per kg. of body weight.

and in the same manner as that used in the studies reported previously (11, 12), was fractionated into these two groups of components in order to investigate the factors responsible for the characteristic

effects upon the leucocytes. The data reported here represent the studies made with the fraction containing sphingomyelins.

METHOD

The sphingomyelins were obtained by the method of Levene (6). The protagon was dissolved in hot glacial acetic acid and was allowed to stand at room temperature. The precipitate at room temperature was treated with acetic acid two more times. The filtrate from the first extraction and the pooled filtrates from the second and third extractions, were carried separately as lots 1 and 2, respectively. Acetone was added to each lot. The resulting precipitates were dissolved at room termperature in mixtures of 5 parts of ligroin (b.p. 30–75° C.) and 1 part of ethyl alcohol. Ninety-eight per cent alcohol was then added and the solutions were filtered. Very little precipitate formed at this stage. The filtrates were allowed to stand over night surrounded by salted ice. Heavy precipitates formed at this temperature. These precipitates were removed by filtration in the ice chest and are designated 1A and 2A, respectively (i.e., fractions A of lots 1 and 2). The filtrates from these failed to yield further precipitate when again packed in salted ice. Acetone was added to them at this temperature. The resulting precipitates are designated 1B and 2B, respectively (i.e., fractions B of lots 1 and 2). Fractions A were creamy pink in color; fractions B, white. The yield was small in each case and did not permit of as extensive experimental investigation as had been hoped. The yield of fraction B was the smaller with each lot. Fractions B at this stage correspond to the sphingomyelin which was extracted by the author for a different series of studies (10) and was found to have an N:P ratio of 1.8:1.

Further purification of the four fractions was carried out separately by crystallization. Each fraction was dissolved in equal parts of chloroform and pyridine over a water bath and allowed to crystallize at room temperature. The mother liquors were withdrawn and the precipitates subjected to fresh solvent. Fractions A were crystallized five times, and fractions B, four times. Fractions B at this stage correspond to the sphingomyelin described by Levene (6).

Experiments were conducted with fractions 1A, 2A and 1B at this

stage of purification. Fraction 1B was purified further by two passages of a solution of the material over columns of Al_2O_3 (Merck, according to Brockmann) as employed by Klenk and Rennkamp (5), except that it was dissolved in equal parts of ethyl alcohol and chloroform for this procedure. The columns were 130 mm. tall. This fraction was analyzed before and after passage over Al_2O_3 for its content of galactolipids according to the technique of Kirk (4).[1] Modifications of the technique by exposure to the $ZnSO_4$ for ½ hour before filtering and by extension of the time required for complete reduction were necessary with this material; and the amount of reduction was determined colorimetrically according to the technique of Folin (2, 3), using a photoelectric colorimeter. Otherwise, the analyses were carried out essentially as described by Kirk. Fraction 1B was found to contain 3.2 per cent of galactolipid before, and 0.12 per cent after, passage over Al_2O_3. This fraction is designated 1B-b before passage over Al_2O_3 and 1B-a after passage.

In conformity with the technique employed in the studies with protagon (11, 12) the specific fraction of sphingomyelin to be used experimentally was dissolved as a stock solution in a mixture of equal parts of chloroform and ethyl alcohol. Aliquots for the amount desired for any given experiment were evaporated over a water bath, emulsified in 5 per cent glucose in strengths varying from 1.0 to 3.5 per cent and sterilized in a steam sterilizer for 2 hours. Injection followed as soon as the emulsion was cooled. The amounts of emulsion injected varied from 4 to 10 cc. (i.e., 53–330 mg. sphingomyelins). The larger doses usually represent the larger volumes. Ordinarily the injections were given slowly in the ear vein of a rabbit over the same length of time and with the same precautions employed with protagon. In one instance the material was given rapidly, and in one, very slowly over a period of 10 minutes. In no case were there indications of untoward reaction.

[1] I take pleasure in thanking Dr. Ann S. Minot, Department of Biochemistry, Vanderbilt Medical School, Nashville, Tenn., and Dr. David Lester, Laboratory of Applied Physiology, Yale University, New Haven, Conn., for advice in performing these determinations. I also wish to thank Miss Margaret Hill, Murfreesboro, Tenn., for the care and patience which she exercised in helping with the extraction of the sphingomyelins.

One male (no. 47) and four female rabbits were used for the studies. They were maintained exactly as described for the rabbits used for the experiments with protagon except that they were kept in much larger cages and in the North instead of in the South.

The blood studies were carried out with the same technique, in all details, as was employed for the experiments with protagon. Therefore, merely the main features will be repeated. Total and differential white and red cell counts were made from the marginal ear veins for 2 or more successive hours as control counts before an injection. The differential counts were made upon 200 or more cells by the supravital technique. Similar studies were then made at each successive hour for 6 hours after injection, beginning ½ to 1 hour after injection. Counts were then made at 2-hour intervals for 24 hours, or until return of the count toward normal semed underway. Counts were frequently made twice a day thereafter for several days.

Two rabbits (nos. 46 and 47) were given one injection only. Two (nos. 44 and 45) were given several injections at widely spaced intervals and with different preparations of sphingomyelins. In one (no. 43) the studies were made only after the animal had been given a series of daily injections which were gradually increased from 10 to 350 mg.

PRESENTATION OF DATA

The complete data are presented in tables I and III, or in charts 2, 3 and 4. The terms granulocytosis or granulopenia and the abbreviation P.M.N. refer to pseudo-eosiniphils wherever they are employed. Only such data are included in the tables as are not prepresented by charts.

Table II was compiled from the data presented in the charts and in table I in order to bring out the magnitude of effect in relationship to the individual rabbit, to dosage, and to specific fraction of sphingomyelin. Table IV presents the time, in relation to the injection, at which the various events among the individual leucocytes usually occurred. It is compiled from the preceding charts and tables and is based on estimates of the interval at which any given event occurred most frequently. At times, the interval recorded represents the actual extremes between the shortest and longest period at which any given change took place. At times, it represents the period at which most

TABLE I

*The Reaction of the White Blood Cells to Injections of Sphingomyelins**

(Absolute numbers in fractions of 1,000)

NEAREST HOUR AFTER THE INJECTION	NUMBER OF RABBIT																							
	43	44			46	47	43	44			46	47	43	44			46	47	43	44			46	47
	Days since last injection						Fraction of Sphingomyelins injected†						Mgm. injected per kg. body weight											
	1		100	19			1A + 2A	1B-b	1B-a	1B-a	1B-a	1B-a	44	30	10	59	56	18						
	W.B.C.						Pseudo-eosinophils						Lymphocytes						Monocytes					
Before injection	8.7	10.2	7.2	7.0	12.4	6.3	2.5	2.5	2.5	2.0	5.0	2.8	5.0	7.1	4.0	4.4	5.6	2.6	0.5	0.3	0.2	0.3	0.8	0.5
½		7.8	7.1	5.5	9.6	7.8		2.4	3.3	1.9	4.0	3.8		4.9	2.6	2.9	4.1	2.8		0.2	0.5	0.2	0.5	0.6
1	6.6						1.9						3.9						0.1					
1½		8.5	6.1	6.1	10.5	6.0		3.5	2.5	3.2	5.8	3.6		4.5	3.0	2.2	3.5	1.2		0.0	0.2	0.0	0.3	0.4
2				6.4						3.0						2.9						0.1		
2½	7.7	8.0	6.9		11.0	7.4	3.9	4.7	3.7		6.3	4.7	3.5	2.9	2.4		3.3	1.3	0.0	0.0	0.0		0.3	0.6
3	5.7			5.5		6.4	1.8			2.6		3.9	3.4			2.1		1.5	0.0			0.2		0.2
4		7.8	5.6	5.3	11.6	6.0		4.4	3.4	2.1	6.0	3.7		3.2	1.8	2.8	3.6	1.6		0.0	0.0	0.1	0.9	0.1
5	4.8	7.2	4.8	5.5	8.5	5.4	2.0	4.1	2.4	2.2	4.8	3.4	2.3	2.5	2.1	2.4	2.9	1.6	0.1	0.2	0.0	0.2	0.3	0.1
6	5.3	7.1	6.9	5.9	10.0	4.8	2.6	4.1	3.4	3.0	5.2	3.1	2.1	2.7	3.1	2.0	3.4	1.2	0.1	0.1	0.0	0.1	0.9	0.1
7	5.1		6.4		8.4		2.6		3.3		5.1		1.7		2.6		2.2		0.2		0.3		0.6	
8		7.3		4.6		6.2		3.9		2.4		3.6		2.9		1.7		1.7		0.1		0.2		0.6
9	6.0		6.5		9.3		3.5		2.6		4.7		1.2		3.4		3.4		0.2		0.2		0.5	
10		8.1		4.9		8.8		2.7		1.8		3.8		5.1		2.5		3.8		0.2		0.1		0.4
11	6.9		8.4		10.4		3.6		3.1		5.0		2.2		4.5		4.6		0.3		0.2		0.3	
12		7.4		5.4		6.2		2.3		2.3		2.4		4.6		2.6		2.7		0.1		0.2		0.3
13					12.7						5.6						5.9						0.3	
14	7.5	7.4		6.8			3.2	3.3		2.1			3.3	3.8		4.2			0.3	0.1		0.2		
15																								
16	8.3						3.6						3.5						0.4					
22		8.8	7.8	8.3	13.3	9.1		2.9	2.0	2.1	5.4	4.2		5.0	5.4	5.4	6.5	3.7		0.2	0.2	0.1	0.7	0.6
23	9.6						1.7						7.4						0.1					
24																								

* This table includes only those experiments which are not recorded by charts.

† See section on methods for full explanation of abbreviations. The designation a or b following fraction 1B is used to indicate whether this fraction was used before (b) or after (a) it had been exposed to adsorption over Al_2O_3.

of the given events occurred and ignores extremes when a single observation at the extreme is considerably out of line. In other words, statement as to the time at which a given event occurs entails a certain amount of variability and must not be taken too specifically. Similar values concerning the reactions of the leucocytes to injections of

TABLE II

Per Cent of Deviation and Time after Injection of the Maximal Variations of Pseudo-eosinophils and Lymphocytes Following Intravenous Injections of Sphingomyelins

NUMBER OF RABBIT	DATE	FRACTION OF SPHINGOMYELIN INJECTED*	DOSAGE	PSEUDO-EOSINOPHILS		LYMPHOCYTES	
				Maximal increase	Time after injection	Maximal decrease	Time after injection
			mgm. per kg.	*per cent*	*hrs.*	*per cent*	*hrs.*
43	12–13–44	1A + 2A	44	56.2	2¼	75.4	9
44	2–12–45	1B-b	30	92.7	2¼	64.4	5
	5–23–45	1B-a	10	46.4	2½	55.4	3½
	6–11–45	1B-a	59	63.1	1½	61.2	8
45	12–29–44	2A	34	107.9	2½	80.3	4½
	3–12–45	1B-b	33	46.3	2¾	72.3	2¾
	5– 9–45	1B-a	31	93.4	3½	75.9	4½
46	5–16–45	1B-a	55	25.3	2½	60.7	6¼
47	5–28–45	1B-a	17	67.6	2½	52.7	6

* See section on methods for full explanation of abbreviations. The designation a or b following fraction 1B is used to indicate whether this fraction was used before (b) or after (a) it had been exposed to adsorption over Al_2O_3.

protagon or nucleotides are also presented in table IV for purposes of comparison. These were reworked from tables I and II of the data published in connection with the reactions to protagon (12).

RESULTS

Certain general statements may be made before the details of the reaction to sphingomyelins are described. The material was well tolerated, both immediately and later, under the different experimental

conditions. This was equally true of rabbit 43 which was given sphingomyelins daily and nos. 44 and 45 which were given various doses at widely spaced intervals. The male rabbit reacted in the same way as the females. The intensity of reaction to equivalent doses varied from rabbit to rabbit, but a given rabbit reacted much the same to the first and later doses, and to large and small doses within the

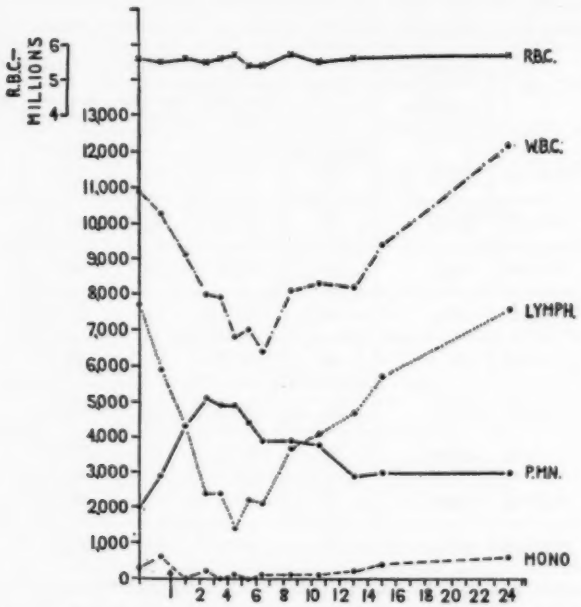


CHART 2. Rabbit 45. Counts of the blood cells following intravenous injection of 34 mg. of sphingomyelins (fraction 2A) per kg. of body weight.

rather narrow limits of these experiments (cf. table II). In other words, no manifestations of tolerance or allergic responses developed in the course of these experiments, and the specific response elicited was relatively independent of dosage. Doses as small as 10 mg. per kg. of body weight were as stimulating as doses of six times that amount (cf. rabbit 44, table II). The reaction was the same to both the A and B fractions of sphingomyelins, and reduction of contaminat-

ting galactolipids from 3.2 to 0.1 per cent, in the case of fraction 1B, caused no change in the character of the reaction (cf. rabbits 44 and 45, table II). The conclusion is therefore drawn that the reaction was not influenced by such amounts of galactolipid as may have been present in those fractions which were not subjected to adsorption.

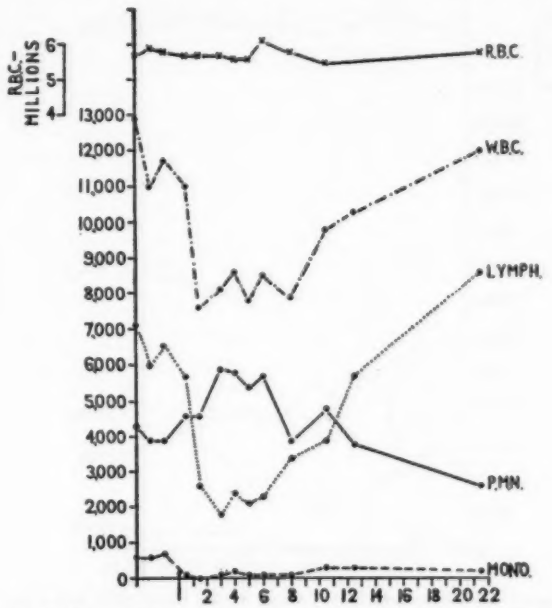


CHART 3. Same rabbit as chart 2. Counts of the blood cells following intravenous injection of 33 mg. of sphingomyelins (fraction 1B before passage over Al_2O_3) per kg. of body weight.

The reaction itself is characterized by moderate granulocytosis and profound lymphopenia. The latter sufficiently dominates the leucocyte counts that there occurred either marked leucopenia or no change in the total white counts (cf. charts 2–4 and tables I and IV). The lymphocytes began to decrease within ½ to 1 hour of the injections, and rapidly reached their lowest levels at periods which varied from 2 to 9 hours of the injections, but which occurred most frequently from 5 to 7 hours after the injections. Thereafter the lymphocytes rapidly

increased to normal within 11 to 15 hours of the injections. They then frequently overcompensated and attained elevated levels by 12 to 24 hours of the injections and returned again to normal between 24 and 48 hours after the injections. The lymphocytic counts at the lowest

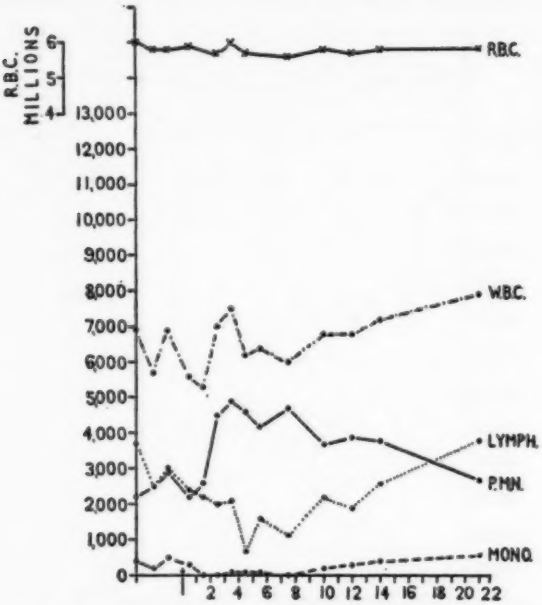


CHART 4. Same rabbit as chart 3. Counts of the blood cells following intravenous infection of 31 mg. per kg. of body weight of the same fraction of sphingomyelin as was used for chart 3 after it had been passed over Al_2O_3 for adsorption of contaminating galactolipids.

levels represent decreases which vary from 53 to 80 per cent of the control values.

The monocytes paralleled the lymphocytes very closely. They frequently disappeared entirely from circulation during the periods of lymphopenia. They returned to normal slightly earlier than did the lymphocytes, and compensatory increases were less frequent.

The granulocytes pursued a reciprocal and usually shorter course than that of the lymphocytes. They began to increase at $1\frac{1}{2}$ to $2\frac{1}{2}$

hours after the injections, reached a peak anywhere from 3 to 12 hours of the injections, but most frequently within 5 hours, and were back to normal within 12 hours of the injections. The increase was always

TABLE III

*Red Blood Counts Following Intravenous Injections of Sphingomyelins**

(Counts in fractions of 1,000)

NEAREST HOUR AFTER THE INJECTION	NUMBER OF RABBIT					
	43	44			46	47
		Exp. 1	Exp. 2	Exp. 3		
Before injection	5,625	5,560	5,496	5,370	5,223	4,526
½		4,993	5,188	4,870	5,253	4,745
1	5,488					
1½		5,125	5,968	5,610	5,620	4,530
2				5,300		
2½	5,760	5,162	5,370		5,145	4,355
3	5,635			4,930		4,690
4		5,490	5,260	5,430	5,435	4,425
5	5,250	5,670	5,020	4,875	5,695	4,355
6	5,360	5,100	5,160	4,925		4,345
7	5,435		5,350		5,080	
8		5,190		5,285		4,490
9	5,355					
10		5,450		4,840		4,005
11	5,445		5,560		4,725	
12		5,060		4,915		4,060
13						
14	6,155	5,270				
15						
16	5,570					
21					5,030	
22		5,268	5,430	5,550		4,405
23	5,395					
24						

* This table includes only those experiments which are not recorded by charts.

moderate (25 to 108 per cent of the control values) and was usually insufficient to compensate for the lymphopenias, so that the total leucocyte counts remained decreased, or, at best, unchanged.

The red counts did not exhibit consistent changes (cf. charts 2–4 and table III). They were elevated at times for the first few hours

TABLE IV

Comparison of Data Following Intravenous Injections of Pentnucleotides, Protagon, and Sphingomyelins

(Summary of: range of dosage; usual interval of time between injection and variations in the leucocytes; range of the per cent of maximal variations of the leucocytes)

MATERIAL INJECTED	RANGE OF DOSE PER KG. BODY WEIGHT	NUMBER OF EXPERIMENTS	INTERVAL IN HOURS BETWEEN INJECTION AND THE EVENTS TABULATED BELOW																			
			Pseudo-eosinophils							Lymphocytes						Monopenia		W.B.C.				
			Neutropenia			Neutrocytosis				Lymphopenia				Lymphocytosis				Leucopenia		Leucocytosis		
			Start	End	Maximal decrease	Start	Peak		End	Start	Maximal decrease		Beginning of return	End	Start	End	Start	End	Start	End	Start	End	
	mgm.		*hrs.*	*hrs.*	%	*hrs.*	*hrs.*	%	*hrs.*	*hrs.*	*hrs.*	%	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*
Pentnucleotides	207 to 242	3	½	3½	63 to 90	4	12 to 15	283 to 510	24+	2	5	95 to 98	9	11 to 13	12 to 20	24+	½	8½	½	5	7	24+
Protagon	23 to 247	14	½	2½	1* to 90	3	3* to 12	33* to 564	9 to 24+	1	2 to 5	40* to 88	7 to 12	7 to 20	none or 10 to 22	none or 24+	½ to 2	8	½	2 to 9	2½ to 7	8 to 24+
Sphingomyelins	10 to 59	9				2	2½ to 3½	25 to 108	12	1	3 to 9	53 to 80	8 to 14	11 to 15	none or 10 to 23	none or 21+	1½	14	½ to 5	2½ to 46	none or 11 to 24	22 to 43

* Some of these rabbits were injected daily with gradually increasing amounts of protagon. This procedure resulted in a lessened intensity of reaction on the part of the leucocytes as the injections progressed. All increases of granulocytes of less than 100 per cent of the control values, and all decreases of lymphocytes of less than 70 per cent of the control values, occurred in such experiments. Under these conditions the maximum increase of the granulocytes usually occurred at an earlier period in relation to the time of injection than in the more intense reactions.

TABLE V

The Reactions of the White Blood Cells to Intravenous Injections of 5 Per Cent Glucose

(Absolute numbers in fractions of 1,000)

in the more intense reactions.

TABLE V

The Reactions of the White Blood Cells to Intravenous Injections of 5 Per Cent Glucose

(Absolute numbers in fractions of 1,000)

NEAREST HOUR AFTER THE INJECTION	NUMBER OF RABBIT																					
	12	15	16	17	18	19	12	15	16	17	18	19	12	15	16	17	18	19	12	15	16	17	18	19
	Cc. of 5 per cent glucose						Weight of rabbit in kg.						Lymphocytes						Monocytes					
	20	15	14	20	20	20	5.3	3.9	3.8	3.8	4.1	3.0												
	W.B.C.						Pseudo-eosinophils																	
Before injection	8.9	12.5	11.6	11.0	6.4	7.5	6.8	7.1	7.1	6.4	2.9	3.6	1.5	3.2	3.5	3.3	2.5	2.6	0.5	1.0	0.7	0.8	0.6	0.4
½																								
1	9.3	11.8	8.5	7.7	6.4	8.4	5.7	5.2	5.3	5.0	3.1	5.5	1.5	4.9	1.1	1.2	2.5	1.8	1.5	0.5	1.2	1.0	0.4	0.3
1½																								
2		10.9	8.2	10.4		7.3		5.6	5.8	6.7		4.2		3.6	0.7	2.4		2.1		0.8	0.9	0.7		0.3
2½																								
3	8.2	10.8	8.2	11.8	7.4	7.8	4.4	6.0	6.2	8.4	4.0	4.2	1.2	3.4	0.9	1.9	2.0	2.5	2.2	0.5	0.8	0.9	0.8	0.4
4	8.3	11.8	7.6	8.0		9.4	6.2	6.1	4.5	5.3		4.9	1.3	3.5	1.5	1.2		1.9	0.5	0.9	0.7	0.6		1.2
5	8.9				5.9		6.7				2.9		1.3				1.9		0.8				0.7	
6		11.0	8.8	12.5		6.6		5.2	5.7	8.4		3.0		4.0	2.2	1.9		2.8		0.9	0.4	1.1		0.4
7	10.5				8.5		7.8				3.7		1.4				2.6		1.1				1.0	
8		10.7	7.8	9.9		10.0		5.7	4.3	5.6		4.7		2.3	2.6	3.5		2.8		1.4	0.6	0.3		0.9
9	8.4				8.4		6.5				3.1		0.8				3.9		1.1				1.1	
10		9.6	7.6	8.1		9.6		6.1	5.5	4.3		5.3		2.3	1.7	2.8		2.0		0.5	0.2	0.4		1.3
11	7.4				9.3		4.2				3.6		1.4				2.9		1.5				1.6	
12		9.6	8.7	4.6		7.6		4.7	4.3	10.3		4.6		3.1	2.9	3.0		1.1		0.7	0.8	0.7		0.9
13	10.6				7.9		6.1				3.5		2.9				1.9		1.5				1.6	
14																								
15	10.2				8.6		7.4				4.3		1.1				1.7		1.6				1.2	
16																								
17	11.4				8.0		6.8				3.3		1.5				3.8		2.7				0.5	
18																								
19	10.1				7.7		6.9				2.8		1.1				3.2		1.9				0.8	
20																								
21																								
22				13.4						9.4						2.3						1.3		
23		14.4	13.8			13.2		6.5	6.5			6.8		6.6	4.1			4.0		0.6	2.1			1.6
24																								

after an injection and decreased in the late hours, but this was not invariable and the reverse also occurred. The striking qualitative changes in the red and white cells that occurred following injections of protagon were not observed in these experiments. The pseudo-eosinophils were often somewhat young during the periods of granulocytosis, as judged by the granules, but evidences suggestive of fragmentations or destruction of any of the cells were lacking.

The control studies consist of the experiments conducted with 5 per cent glucose and with egg lecithin that were reported in the studies with protagon (table IV and charts 7 and 8, ref. 12). The same is true of the studies with nucleotides (table III and chart 6, ref. 12) and with protagon (table II and charts 1–5, ref. 12). Table V presents the hourly counts on the six rabbits given glucose. These counts were not published previously. Four of the rabbits given glucose exhibited no characteristic changes in the blood counts within 24 hours of the injections. Two (nos. 16 and 17) presented reactions which were similar, though less active, to those obtained following injection of sphingomyelins. There were no changes in the monocytes in any case.

Unlike the reactions to sphingomyelins, the immediate reaction to injections of lecithin consisted of mild increases of both granulocytes and lymphocytes. Low-grade lymphopenias developed $1\frac{1}{2}$ to $2\frac{1}{2}$ hours after the injections, however. They were transitory in two of the experiments but more prolonged in the other two rabbits (24 and 28). The reactions of these two are therefore suggestive of the lesser reactions to sphingomyelins, although they differ in duration and in relation to the time of injection. Monopenias occurred in all.

DISCUSSION

The response of the pseudo-eosinophils to intravenous injection of sphingomyelins is characteristically different from that to injection of protagon, with a consequent very different leucocytic curve (cf. chart 1 with charts 2–4, and table IV). The period of granulopenia that follows immediately upon injection of protagon is completely lacking following injection of sphingomyelins. The period of granulocytosis following injection of sphingomyelins begins earlier than after injection of protagon, or at least becomes evident earlier, perhaps because it

is not necessary to first overcome a granulopenic state. It reaches a peak at about the same time as in the less reactive of the protagon experiments, although far earlier than in the more dramatic responses to protagon, but the height of the peak is much less than after protagon. In the case of protagon the peaks represent increases of 33 to 564 per cent of the control values while the peaks of the granulocytic reaction after the injections of sphingomyelins represent increases of only 25 to 108 per cent. Furthermore, all increases of less than 100 per cent of the control values in the protagon experiments occurred in animals in which the capacity for reaction had decreased consequent upon a series of preceding injections. In summary, then, the granulopenic phase characteristic of the reaction to protagon is lacking in the reaction to sphingomyelins; and while a granulocytic phase occurs in the reaction to sphingomyelins, it is markedly less intense and prolonged than in the reaction to protagon. It is probable, therefore, that the granulopenia and most of the ensuing granulocytosis that follow injection of protagon are due to the high content of galactolipids in the protagon, or to some substance carried with that fraction.

The passage of one fraction of sphingomyelins (fraction 1B) over Al_2O_3 was carried out in order to determine if that degree of granulocytosis which does occur after injection of sphingomyelins might be due to contamination with galactolipids. Since the content of galactolipids was reduced by this process from 3.2 to 0.1 per cent without change in the reaction of the granulocytes, it is concluded that the granulocytic response found characteristically after injection of the different lots of sphingomyelins is inherent in the response to sphingomyelins, and that it differs from the response of the same cells to protagon in the absence of a granulopenic phase, in an earlier onset of granulocytosis, a lesser degree of granulocytosis and an earlier return to normal.

In contrast to the difference in reactions of the granulocytes after injections of sphingomyelins and of protagon, the reactions of the lymphocytes are so similar that it seems probable that the lymphocytic response to protagon is due entirely to the component of sphingomyelins. The time that the lymphopenias begin after injection of both substances (within 1 hour), the time of the lowest counts (about 5 hours), the per cent of decrease at the lowest point compared to the

control counts (50 to 80 per cent), and the average time of return to normal (about 11 hours) are within the same limits.

As in the case of the lymphocytes, the reaction of the monocytes to the two substances is similar in timing and degree. By the same reasoning, therefore, the monopenia which follows injection of protagon may be considered to be due to the content of sphingomyelins. The parallelism between the reactions of the lymphocytes and monocytes with each substance is noteworthy, and would seem to indicate a similar action upon, or by, both types of cells.

The total white counts following injection of sphingomyelins differ from those following injection of protagon, due, actually, to the differences in the grades of granulocytosis, since the reactions of the lymphocytes and monocytes are similar with both substances. While the total white counts exhibit sharp increments following injection of protagon, they suffer sustained depression, or do not fluctuate from normal, following injection of sphingomyelins, dependent entirely on whether the grade of lymphopenia outweighs or equals that of the moderate granulocytosis due to sphingomyelins alone. In this respect, graphs of the total white blood counts following injections of the two substances are very different (cf. chart 1 with charts 2–4).

Analysis of the control studies with glucose or with lecithin lead to the conclusion that the effects from the injections of sphingomyelins are due to the latter lipoids specifically and are independent of the simultaneous injection of the menstrum (5 per cent glucose) or of those factors which sphingomyelins and lecithins have in common (i.e., colloids, lipoids, phosphatides, and phosphoric acid-choline linkage). Since much larger volumes of glucose were employed for the control injections of glucose than for the injections of sphingomyelins, and since the reactions which followed the control injections were sporadic and mild, it is obvious that the reactions to the emulsions of sphingomyelins are specific and not due to the emulsifying menstrum. There are features in the reactions to the control injections of egg lecithin, on the other hand, which indicate that that lipoid carries an undercurrent of related activity. This is so much less vigorous and less constant in effect, however, than the action of sphingomyelins, even though considerably greater amounts of lecithin were employed than of sphingomyelins, that there seems little doubt of the specificity of reaction to the latter phosphatide.

The reactions of the leucocytes to sphingomyelins and, in particular, that of the lymphocytes, are strikingly similar to the reactions reported by Dougherty and White (1) and by Reinhardt, Aron and Choh (8) following injections of pituitary adrenotrophic or adrenal cortical hormones. The period of maximal decrease of the lymphocytes is somewhat earlier following injections of sphingomyelins than found by these workers, but the time of onset, the acuteness of onset, the degree of lymphopenia, the duration of lymphopenia, the quickness of recovery, once the cells begin to return to the circulation, the tendency to succeeding lymphocytosis and the overbalance of lymphopenia to granulocytosis with consequent prolonged leucopenia—all these present a picture that is strikingly similar in the two instances. The changes in the red cells noted by Dougherty and White occur at times after sphingomyelins, but not invariably (cf. table III and charts 2–4). On the other hand, monopenias were not recorded in the case of the workers with pituitary and adrenal hormones. Since the supravital technique lends itself particularly well to differentiation of monocytes from other mononuclear cells, and the count of monocytes in fixed preparations is usually low and variable, it seems probable that decrease in monocytes may not have been sufficiently striking by fixed technique to attract attention. As is discussed by Dougherty and White, the differences in time of maximal lymphopenias in these different groups of experiments may as well be due to differences in route of injection, to speciae injected, or to dosage as to the differences in material injected. On the other hand, they may be representative simply of difference in presentation of data. The data presented for sphingomyelins represent findings in individual animals, and those values vary considerably among themselves. The values presented in the literature represent those obtained from pooled observations.

There is no evidence in the studies reported here as to how the effects of sphingomyelins upon the lymphocytes are brought about: as to whether they occur through action upon the pituitary-adrenal complex, upon the unknown mechanisms concerned with the action of adrenal cortical hormones on lymphocytes, or upon lymphocytes directly. There is likewise no indication as to whether the lymphocytes are destroyed or simply attracted into the tissues by some mechanism other than destruction. Whatever may be the explanation of the disappearance of lymphocytes from the blood stream, it would

seem that the course of events thereafter is similar to that following stimulation of the pituitary-adrenal complex, and most probably represents the time required for regeneration at the sources of formation.

The effect upon granulocytes inherent in the reaction to sphingomyelins, irrespective of the superimposed effect obtained with protagon, is of interest. As described above, it is similar to the effect of pituitary-adrenal stimulation upon the granulocytes. It is initiated at a slightly later period than the onset of the lymphopenic phase. Wiseman, Doan and Erf (13) suggest that a fundamental reciprocal relationship exists between lymphocytes and granulocytes and support the hypothesis by various clinical and experimental illustrations. Sayers, Sayers, Fry, White and Long (9) believe that the reaction following administration of pituitary adrenotrophic hormone is elicited by a wide variety of comparable stimuli. The possibility that a certain degree of granulocytosis is reciprocally related to loss of lymphocytes from the circulation seems tenable. On the other hand, the experiments with nucleotides and with protagon, in contrast to the experiments with its component of sphingomyelins, indicate that stimulus to granulocytes may far outrun that which is related to decrease of lymphocytes only, and vice versa.

Since the reaction to protagon has been shown to be identical to the reaction to nucleotides (12) the possibility arises of a double action from nucleotides similar to that from protagon. Both substances elicit the granulopenic phase and the marked and prolonged granulocytic one that are found to be lacking in the reaction to sphingomyelins alone. The peak of granulocytosis is greater and occurs later after injection of nucleotides than is true in many of the less active responses to protagon. The less active responses, however, usually occurred in animals that had been injected repeatedly and had developed a lessened reactivity to protagon. The time required to attain the peak of granulocytosis following injections of protagon tended to increase in proportion to the intensity of the granulocytic reaction, and in such instances the similarity to the reaction to nucleotides is more pronounced. The degree of lymphopenia and the interval of time between injection and maximal depression of lymphocytes were somewhat greater after injections of nucleotides than after

injections of protagon. Monopenias occurred after injections of nucleotides, as well as after injections of protagon or sphingomyelins, but they were less intense and less prolonged. Since the reaction to protagon can be broken into separate components, i.e. (*1*) that concerned with lymphocytes, which, in turn, is like that elicited by sphingomyelins and by the pituitary-adrenal complex, and (*2*) that concerned with granulocytes which, in turn, is superimposed upon the reaction of granulocytes inherent in the response to sphingomyelins or to the pituitary-adrenal complex, it seems probable that the reactions of the different leucocytes to nucleotides may represent comparable responses to different pharmacologic features of the drug.

SUMMARY

1. Intravenous injections of protagon obtained from beef brain were shown to affect the circulating leucocytes in the same way as do nucleotides (12). Sphingomyelins have been extracted from this protagon and used in experiments similar to those conducted with protagon. Discussion is presented of their action on the circulating leucocytes and of their probable share in the reactions to protagon. The differences in reactions to these two substances are shown by comparison of chart 1 with charts 2–4. Summary of the differences follows:

A. The granulopenic phase, which characterizes the response to intravenous injection of protagon, is absent in the response to intravenous injection of sphingomyelins.

B. Low-grade granulocytosis follows injection of sphingomyelins, but the marked stimulus to granulocytosis, which is characteristic of the reaction to protagon, is lacking in the reaction to sphingomyelins. The granulocytoses begin within 1½ hours of the injections and reach their peak in about 5 hours.

C. Sphingomyelins affect the lymphocytes in the same manner as does protagon. This is characterized by:

(1) a prolonged period of lymphopenia which begins within 1 hour of the injections, reaches a minimal count at about 5 to 7 hours of the injections, and continues at low levels until the lymphocytes begin to increase in circulation at about 9 hours after

the injections. The minimal counts represent reductions of 50 per cent or more of the control counts;

(2) return of the lymphocytes to normal about 11 hours after the injections;

(3) a subsequent period of lymphocytosis which terminates 24 to 48 hours after the injections.

D. A period of monopenia begins at the same time after injection of sphingomyelins as after injection of protagon. It continues slightly longer. It coincides with the period of lymphopenia in time of onset but recovery is slightly earlier.

E. In contrast to the leucocytosis, which follows injection of protagon, the total white count following injection of sphingomyelins suffers sustained decrease, or remains normal.

2. The effects of intravenous injection of sphingomyelins upon the blood cells, and in particular upon the circulating lymphocytes, are similar to those produced through the pituitary-adrenal complex of hormones.

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ASTHMA—AS OBSERVED OVERSEAS IN A GENERAL HOSPITAL IN THE SOUTHWEST PACIFIC AREA—WITH SPECIAL REFERENCE TO RELATIONSHIP OF TROPICAL SERVICE TO ONSET AND RECURRENCE

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Asthma has proved to be one of the important causes of chronic disability in the Armed Forces serving in the Southwest Pacific Area. It has also been one of the chief medical conditions necessitating the return of army personnel from this hospital to the United States as unfit for further duty in this area. That asthma should recur or develop to a greater extent in the Armed Forces, either in the United States or overseas, than in the same age group among the civilian population was not unexpected. The extremes of climate, increased exposure to dust and pollen, strenuous physical exertion and the emotional strain of military life would favor the recurrence, or aggravation of mild asthma, and, furthermore, the development of new cases.

That environmental conditions peculiar to the tropics were especially prone to aggravate or induce asthma, was recognized soon after our military units occupied certain islands in the SWPA. Prior to this war, our troops in such large numbers have not been called upon to serve under the rigorous physical and climatic conditions encountered in the Pacific Island campaigns. To the author's knowledge, past or current medical literature and standard treatises on tropical diseases contain no comment on the unfavorable effect of tropical conditions on the asthmatic state, nor likewise on the tendency for asthma to develop in healthy individuals who have never previously exhibited such symptoms.

It is obvious that the military aspects of this whole question are of considerable importance, and further studies and reports on this subject, especially from an overseas area, seem desirable. In the United States the several allergic conditions observed in military personnel have been receiving increased attention. In Massachusetts, Hyde and Kingsley (1) surveyed the incidence of allergic conditions in 60,000 inductees and found that 0.8% were disqualified because of some al-

lergic complaint or abnormality. Of these, bronchial asthma represented 75%. French and Halpin (2) recently summarized the data obtained from a series of allergy clinics which they established in the Fourth Service Command. They emphasize that the allergic disturbances cause considerable disability, and are the basis for discharge from service in significant numbers. However, specific treatment which they have instituted, has proved feasible, and they have been able thereby to return many soldiers to duty. More recently Alford (3) reported on 100 soldiers with bronchial asthma observed at the Percy Jones General Hospital. The series represented 10% of medical admissions. 23 had developed asthma while serving in the Pacific theater. There was a history of hay fever in 18, and almost all presented positive skin reactions to stock dust but a higher percentage reacted to extracts of dust obtained from the Pacific theater. The latter extracts were clinically more potent, and the protein nitrogen content thereof 20 times greater than that possessed by extracts of dust obtained in the United States. Dust and dampness were emphasized by the soldiers returned from the Pacific Area as the two factors most likely to precipitate attacks of asthma, a statement which the present study verifies.

Asthma, hay fever, urticaria, and angioneurotic oedema have all been observed frequently in the order named, but the possible causes of and the disability occasioned, particularly by asthma, aroused our interest and prompted the present report. Over a two year period ending 31 July 1944 the diagnosis of asthma was made on 352 patients at this hospital representing 1.2% of total admissions. Of these, 209 were examined in detail in the allergy clinic, and the following data have been compiled from their records. It was considered of interest to divide the series for comparative reasons into two groups: (1) asthma, the onset[1] of which occurred prior to service, and (2) onset after entering service. Numerically the two groups are essentially equal, although no attempt was made to select cases. For sake of brevity the two groups will be considered for the most part together.

Current entry into Service, and Source of Admission: 136 were inducted, 51 enlisted, 13 were federalized with the National Guard, and

[1] The word onset as used in this study means specifically the original or primary attack of asthma.

8 were officers, A. U. S. 109 were admitted by transfer from other hospitals for further study and disposition as regards duty. A comparatively large number were admitted by transfer from unit dispensaries, or through the Base Dispensary while on leave in this area. 5

TABLE I

Age at onset, personal history of hay fever, family history of asthma and/or hay fever, and clinical form of asthma

		107 CASES ONSET PRIOR TO SERVICE	102 CASES ONSET DURING SERVICE
Age at onset	0–10	48	0
	10–20	37	3
	20–30	19	73
	30–40	3	23
	40–50	0	3
Personal history of hay fever	Seasonal	24	10
	Perennial	35	33
	Combined seasonal & perennial	15	5
		—	—
		Total: 74 or 70%	Total: 48 or 47%
Family history of asthma and hay fever	Asthma	27	11
	Hay Fever	25	17
	Asthma & Hay Fever	7	2
		—	—
		Total: 59 or 50%	Total: 30 or 28%
Clinical type of asthma	Perennial	47	102
	Seasonal	Summer: 15	
		3	
		Winter: —	
		18	
	Combined Seasonal & Perennial	42	

were admitted from the Detachment of this Hospital, and 2 were treated as out-patients in the Allergy clinic.

Age at Onset, Incidence of Hay Fever in the Personal History, of Asthma and Hay Fever in the Family History and the Clinical Form of Asthma: Table I shows that 85, or 79% of the 107 cases of asthma of Group I which began prior to service developed before the age of 20,

the period in life in which the cause of asthma in an overwhelming percentage, is generally accepted as due to specific allergic factors. By comparison only 3 of 102 cases in Group II, in which symptoms began after entering service, started during the same period. An allergic personal and/or family history of hay fever or asthma was obtained in a great majority of Group I (onset prior to service) but in less than one-half of Group II (onset after entering service). In Group I a personal history of hay fever was elicited in 75 or 72%, and a family history of hay fever and/or asthma in 59 or 57%, compared to 48 or 47% and 30 or 29% respectively, in Group II. Of Group I, 47 gave a history of perennial asthma, 18 of the seasonal type (15

TABLE II

Effect of tropical conditions on asthma existing prior to tropical service

LOCATION AT ONSET	NO. OF CASES	INCIDENCE OF AND GEOGRAPHIC LOCATION OF AGGRAVATION OR RECURRENCE		
		U. S.	Australia	Tropics
United States	126	38	31	111 (of 119 serving in)
Australia	17		5	8 (of 11 serving in)
Tropics	66		1	
Totals	209	38	37	119 (of 130 serving in)

accentuated during the summer and 3 during the winter), and 42 of the perennial form with seasonal summer accentuation. Observations on Group II covered too short a period to permit such a classification; the majority, however, presented a history of chronic asthma of varying severity, or of recurring attacks not limited to any particular season of the year.

Geographic Location at Onset: All but 2 of the 107 cases of Group I started, as would be expected, in the United States; the other 2 noted initial symptoms in Panama. Of Group II, 21 or 20% began in the United States, 17 or 16% in Australia (temperate zone, south of the 21st parallel), and 64 or 64% on tropical islands in the Southwest and South Pacific Areas. (See Table II for combined figures.)

The Effect of Tropical Conditions on Asthma Existing Prior to Tropical Service: Soon after this Hospital opened, a comparatively large group of patients was admitted following evacuation from tropical

islands because of asthma. All dated onset of initial attack or recurrence of same soon after entering the tropics. As time went by, this history became very familiar. Reference to Table II illustrates the striking aggravating effect of tropical conditions on asthma. 119 or 91%, of the 130 patients who served in the tropics experienced aggravation or recurrence, whereas, only 31 or 24% experienced the same in Australia (temperate zone), 20 prior to and 11 after a tour of tropical duty. Only 11 or 9% did not experience aggravation or recurrence during tropical service varying from a few months to over a year, although mild symptoms persisted.

Duration of Tropical Service Prior to Onset of Asthma and Aggravation or Recurrence: The interval between arrival in the tropics, and the date of recurrence or aggravation was obtained from 74 of 119 patients, and reference to Table III shows that in 66 or 89% this happened

TABLE III

Relationship of duration of tropical service to aggravation and/or recurrence and to onset

MONTHS IN TROPICS	½	¾	1	2	3	4	5	6	7	11	15	18	TOTAL
Prior to aggravation or recurrence	12	17	17	10	6	1	7	3	0	0	1	0	74
Prior to onset	3	11	13	14	5	7	2	3	2	0	0	1	61

within three months after arrival. In 61 of 64 patients, whose asthma originated in the tropics, 46 or 75% developed within the same period. 29 recurrences came within the first two weeks, compared to 14 new cases originating in the same period. In general the interval prior to recurrence or aggravation was usually less than the interval prior to the original development of symptoms. This observation is consistent with the natural history of asthma or other allergic conditions; namely, recurrence or aggravation of allergic symptoms is produced more rapidly in the sensitized than in the non-sensitized individual, or at least in individuals whose tissues through heredity are hypersensitive but for reasons still obsure have never clinically manifested allergic symptoms. Recurrence, therefore, would correspond to the immediate reaction of anaphylaxis; whereas, original onset would represent the development of the anaphylactic or hypersensitive state. Further reference to this suggestion will be found in the discussion on etiology.

Monthly Incidence of Onset and of Aggravation or Recurrence: The monthly incidence of aggravation or recurrence and of onset is presented in Table IV. It can be seen that there is little if any seasonal variation in either onset or aggravation, either in the tropics or in Australia. 104 patients were able to recall the month of recurrence or aggravation in the tropics; 28 or 27% gave the specific month while serving in Australia; and 61 or 98% of 64 who developed their primary attack in the tropics recalled the month of onset. Examination of the table shows an apparent increase both of aggravation or recurrence and of onset during April and May. The figures include, however, 41 cases admitted simultaneously to the hospital from tropical islands in the South Pacific Area. In this group, 7 recurrences started during

TABLE IV

Monthly distribution of aggravation or recurrence and of onset to illustrate absence of seasonal variation

MONTH OF YEAR	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	TOTAL
Aggravation or recurrence in the tropics	3	5	6	15	18	7	11	6	6	6	10	11	104
Aggravation or recurrence on the mainland of Australia	4	3	4	0	1	7	3	2	3	0	1	0	25
Onset in the tropics	2	1	5	8	16	3	8	8	2	1	1	6	61

April, 9 during May, 1 in March, 3 in June, and 1 in July, following tropical service of 2 weeks in 4, 1 month in 5, 2 months in 8, and 3 months in 4. Likewise, with regard to onset in this same group, 3 began in April, 12 in May, 2 in June, and 2 in July, of which 6 began 2 weeks, 5 one month, and 9 two months after arrival. If these figures are taken into consideration the monthly distribution would present a more even curve throughout the year. For example: if arrival in tropics was 2 months later for each individual, the corresponding high points in the curve would be two months later than indicated; therefore, date of arrival rather than seasonal enviromental factors controls the monthly distribution of recurrence and onset. This fact will be considered later when the question of etiology is discussed.

Results of Skin Tests with Extracts of Pollen and Inhalant Dusts: Table V lists the incidence of positive skin reactions in Groups I and II

on whom skin tests were actually done. Pollen extracts employed for testing and treatment were obtained from Commonwealth Serum Laboratories, Commonwealth of Australia, and included Kentucky Blue Grass, Capeweed, Plantain, Paspalum, Rye Grass (the important pollens in southern and eastern Australia); Inhalant Dusts including House Dust, Chicken Feathers, Wool, Kapok, Cottonseed, and others were obtained in part from the Laboratories mentioned, and part were contributed to the Hospital in lyophilized form by Sharpe and Dohme, Philadelphia. All tests were performed intradermally with approximately 0.02 cc. of extract, containing 1,000 protein nitrogen units per cc., except for a few patients whose clinical histories suggested unusual

TABLE V

Results of skin tests to extracts of pollen and inhalant dusts

ONSET	INHALANTS		POLLEN	
	No. tested	Positive	No. tested	Positive
Onset prior to service	86	74–86%	48	35–73%
Onset during service	76	46–60%	35	22–62%

sensitivity, when a solution of 100 protein nitrogen units per cc. were used. In some, presenting a characteristic history of seasonal hay fever and asthma, tests were not considered essential and were not done. Criterion of positive skin sensitivity was based on appearance of typical wheal-erythema reactions at sites of at least three of each group of substances employed.

Of 86 or 80% of patients in Group I in whom asthma started prior to service, 74 or 86% reacted positively to the inhalants, and of 48 tested with the pollens, 35 or 73% reacted positively, compared to 46 or 60%, and 22 or 62% respectively, of individuals of Group II, in whom asthma started during service. The higher incidence of skin reactivity in Group I would be expected in view of the higher incidence of clinical allergy in the personal and family histories of this group, compared to Group II, as recorded above.

Etiology: It is well recognized that asthma may be due to several causes, and in many instances, the etiology is unknown. The presence in the individual of an hereditary allergic diathesis is, however, gener-

ally accepted as the most important predisposing condition. The development of asthma in the patients presenting a history of seasonal or perennial hay fever was not unexpected or surprising, as it is well known that approximately 50% of individuals with such a history develop asthma at one time or another during life. Regarding the etiology of the patients in this series in which this history was lacking, it was postulated that they possessed through heredity a tendency

TABLE VI

Correlation in individual patients of hay fever and/or asthma in the family history, of hay fever in the personal history, and of skin reactivity to antigens used in this study

GROUP	SKIN TESTS	F.H.*	P.H.†	P.S.T.‡	F.H. P.H.	F.H. P.S.T.	P.H. P.S.T.	F.H. P.H. P.S.T.	NEGATIVE	TOTALS
I	Yes	3	2	12	3	7	25	30	4	86
	No	4	4		12				1	21
II	Yes	5	6	10	4	6	19	11	16	77
	No	2	8		2				13	25
Totals.....		14	20	22	21	13	44	41	34	209
Onset in tropics	Yes	4	1	4	2	5	11	9	8	44
	No	3	5		2				10	20
Totals.....		7	6	4	4	5	11	9	18	64

* Family History.
† Personal History.
‡ Positive Skin Test.

to develop manifestations of hypersensitivity or actual tissue hypersensitivity as revealed by testing the skin with the antigens enumerated above.

Although Table I shows the incidence of hay fever in the personal history and of hay fever and/or asthma in the family history, it does not correlate in the individual these two phenomena with the results of skin tests which as stated above may reveal the presence of tissue hypersensitivity. Table VI records such an analysis and includes as a special group, the individuals in whom asthma originated in the tropics. The cases are separated depending on whether or not skin tests were made.

It is apparent from the table that in most of the patients a family or personal history of allergy and/or skin sensitivity were found. 175 or 83% of the 209 patients presented one or more of the three factors. The only essential difference between Groups I and II is that a larger number in the latter group lacked all three factors. This is probably explained by the higher incidence of infection considered as causal in Group II (see below). The data on the patients in whom asthma originated in the tropics differs in no way from the series as a whole, and further comment on this group is unnecessary.

Although such an analysis reveals the high incidence of allergy in the family or personal history and of skin sensitivity to certain allergens, the immediate cause or causes precipitating asthma in the series in many instances is not clear; undoubtedly, they are multiple rather than single. Aside from pollen and other inhalant dusts discussed below, they include such factors as damp, humid weather, excessive rain, marked diurnal variation in daily temperature, severe physical exertion, emotional tension, and infection of the upper and lower respiratory tract—all of which, as is well known, may induce attacks of asthma in hypersensitive individuals. Many attributed onset to "head" or "chest colds," others to damp, humid weather, so common in the tropics; and a few stated that the aroma of molds, which grow luxuriantly and quickly, induced attacks. In a few chills and fever of malaria initiated attacks, and one case developed asthma during convalescence from typhus fever. Of all the suspected immediate causes, humid, damp weather prevailing particularly at night, in the tropics at least, was cited most often by the patients.

As regards the significance of pollens and other atmospheric particles, detailed pollen surveys of the tropical islands in the Southwest Pacific Area, though highly desirable, have not been reported; hence, little is known about this subject. Young, Cook and Kawasaki (4) in a report on allergic rhinitis and asthma observed in Hawaii in 1943, found pollen in the air throughout the year, and symptoms caused thereby are perennial. Grass pollen, pollen from the Kiawe or algeroba tree, and environmental dusts were considered the important causes of rhinitis and asthma. In Australia, according to information published by the Department of Health, based on pollen surveys in Melbourne by Sharwood (5), and in Adelaide by Mercer (6), atmospheric pollen in

these areas prevails throughout the year, but is only of real significance during eight months, from August to March inclusive, which corresponds to the hay fever season. Clinically, the same applies to the Sydney area, although pollen counts by Phillips (7) cover only the period from the 1st of September to the 31st of December. As the equator is approached, it is undoubtedly true that pollen is perennial, and since onset and recurrence was perennial, and not seasonal in this

TABLE VII

Tabulation of probable causes of asthma based on clinical history, family history, and clinical examination, including skin reactivity to pollens and environmental dusts

	ALLERGIC			INFECTION		CAUSE UNDETERMINED		
						Skin tests		
	Pollen	Pollen & Dusts	Dusts	U.R.I.	L.R.I.	Positive	Negative	Not done
Group I onset prior to service	2	49*	37	5†	4‡	3	7	
Group II onset after entering service	0	15	12	16	4 B—2 Pn—2	18 Mal—2	18	18 T.C.—3 Mal—1
Totals	2	64	49	21	8	21	25	18

* 12 complicated by upper respiratory infection, or polyps, as follows: 3 by infection of sinuses; 2 by sinusitis with polyps; 5 by chronic tonsillitis; 1 by tonsillitis, chronic and nasal polyps; 1 by nasal polyps without evidence of infection.

† 3 gave history of hay fever.

‡ 1 gave history of perennial allergic rhinitis; one of hay fever.

B—Bronchitis; Pn—Pneumonia; Mal—Malaria; T.C.—Tonsillitis, chronic.

series, pollen and other inhalant dusts, including many spores may well play an important causal role.

After an evaluation of all data, the probable immediate precipitating cause or causes of asthma in this series are tabulated in Table VII. In Group I, 2 cases were considered as being directly related to pollen alone; 49 to pollen and inhalants combined; 37 to inhalants alone; 5 to upper respiratory infection; and 4 to lower respiratory infection. In 10, probable causal factors could not be determined; but, of these, 3 gave positive skin tests to the pollens and inhalants, and 7 were negative. Of Group II, in which asthma started after entry into service,

and including the 66 that started in the tropics, none of these cases was considered as due to pollen alone; 15 were considered as directly related to pollens and inhalants combined; 12 to the inhalants alone, and 20 to respiratory infections. In 54 cases of this group probable causes could not be determined. Of the latter, 18 gave positive skin reactions, 18 were negative, and on 18 tests were not done. The etiological significance of damp, humid weather, emotional tension, severe physical exertion, combat duty and other conditions is not clear; all would, however, tend to aggravate symptoms or even precipitate attacks in any patient. They are considered, however, as contributory causal factors, but not basic and they are therefore not classified in the table.

In summary then as regards etiology, the combined statistics on both groups indicate that through inheritance a state of tissue hypersensitivity was present in the majority of cases; in addition and superimposed on this state of hypersensitivity is a group of conditions as enumerated above, which encountered by the soldier in active military service could induce attacks of asthma depending on the degree and duration of exposure to any one or a combination of these conditions. One probable precipitating condition which has only been alluded to and has not been included in the table, is emotional tension. This is undoubtedly of significance, especially in the exaggeration of symptoms, but it is difficult to assess, and time did not permit a detailed study by the psychiatric consultant.

Duration of Disability: In Group I, the minimum days lost from duty in hospital was 5, the maximum, 224 and the average 60.24 with a total of 6325 days, compared to 6, 181, 57.71, and 5835 respectively in Group II. The duration of disability measured in hospital days in an overseas area is accounted for in part by the period elapsing between the decision of Disposition Boards to recommend evacuation to the United States and the actual time that transportation becomes available. Though numerically small compared to other diseases observed in this area, the average disability per patient equals if not exceeds any other medical disturbance except the major psychoses. Even for mild cases the total hospital days assumed large proportions. Such cases are frequently subject to acute attacks necessitating brief admissions, where under relatively controlled, or at least improved environment, rapid improvement obtains and the patient is discharged to

duty. When symptoms become chronic, however, but not incapacitating, moderate to even marked improvement in hospital may be noted, and the question then of deciding duty status in particular cases may be difficult. When such duty could be limited to Base commands in temperate zones, a small percentage were able to continue duty without undue loss of time, although, in many, recurrences of varying severity and duration developed and necessitated return to the United States, as the following paragraph will illustrate.

Disposition: As stated above 352 or 1.2% of the total admissions to the Hospital over a two year period were diagnosed as asthma. The total number of cases of all types returned to the United States from this Hospital was 2980 of which 290 or 9.1% represented cases of

TABLE VIII

Disposition of 209 cases of asthma

	TO U. S.	DUTY			
		Full duty		Limited duty	
			To U. S.		To U. S.
Onset prior to service, 107 cases	82	9	2	16	5
Onset after entering service, 102 cases	75	9	0	17	8
Totals	157	18	2	33	13

asthma. Disposition of the 209 presented in this paper is tabulated in Table VIII. Of the 107 cases in Group I, (onset prior to service) 82 were evacuated to the United States, 9 were discharged to full duty and 16 were reclassified to limited, non-tropical duty. Later, after varying periods of service, 2 on full duty and 5 on limited duty were readmitted and evacuated to the United States. 89, therefore, of 107 cases in Group I were ultimately evacuated from this theater, 18 remained on duty (7 on general service and 11 on limited duty). Of 102 cases in Group II, 75 were evacuated to the United States; 9 were discharged to full duty, and 17 to limited, non-tropical duty, of which 8 were eventually returned to the United States because of aggravation of their symptoms. Total figures on both groups are: 172, or 82%, evacuated to the United States; 36, or 17%, continued on duty; 16 on

full duty and 20 on limited duty status. It is possible that some of the patients discharged either to full or limited duty were eventually admitted to other hospitals and evacuated to the United States. In this respect, 6 of the limited duty patients returned to the United States had previously been placed on this status at another General Hospital.

It is thus seen that when the asthmatic process has become established, the resulting disability represented by days in hospital in this theater reaches significant figures; and, furthermore, for one disease entity, the percentage who were considered as unfit for duty in this theater and evacuated to the United States is strikingly high.

Treatment: In addition to treatment directed toward relief of immediate symptoms, 10 surgical procedures were performed on 4 patients. These included tonsillectomy and adenoidectomy, submucous resection and nasal polypectomy. Whether or not the course of asthma was modified thereby cannot be stated. The paucity of outspoken infections of the upper respiratory tract and of hypertrophy of nasal mucous membranes requiring surgical procedures was striking. In addition to surgical measures a desensitization program was considered and eventually instituted, based on the possibility that at least some of the patients so treated could be retained in this theater for essential service in some capacity. 38 patients were desensitized, 28 to inhalant dusts, 3 to pollens and inhalant dusts combined, and 7 to histamine.

Pollen and dust treatment consisted of subcutaneous injections beginning usually with 10 protein nitrogen units of pollen, and 100 units in the case of inhalant dusts. The total number of units given to each patient varied from 200, to 10,000 units. Therapy was stopped when dosage of 5,000 to 10,000 units was reached, or in many instances when patients were evacuated to the United States after failure to respond to treatment was evident. In some the dosage obtained was less than would be expected to influence symptoms but for sake of completeness and to avoid contention that the results as reported are based on special selection of material they are included.

Histamine was given subcutaneously beginning with 0.001 mgm., increasing to point of tolerance. This was usually 0.1 to 0.2 mgm. Asthmatic symptoms in these seven patients, whose skin tests were

negative, seemed more related to physical factors such as climatic conditions, attacks being induced by humid, or damp cool weather.

Results of desensitization in any group of asthmatic patients is difficult to appraise. What might be construed, however, as the results of such therapy is indicated by the eventual disposition of each individual patient so treated. 23 of the 38 patients treated were eventually discharged to duty, 5 to full and 18 to limited non-tropical duty. Of these, 2 and 8, respectively, were eventually returned to the United States; only 13 of the 38 patients treated by desensitization remained, to my knowledge, on duty in this theater. The four patients on whom nasal surgery was done are included in the group returned to the United States.

Discussion: Our attention was originally called to this subject when the unfavorable effects of tropical conditions on asthma became apparent soon after our troops occupied certain tropical islands in the Southwest and South Pacific Areas. As more and more cases were observed, general aspects of the whole question assumed considerable importance and prompted the present study.

The rapidity with which recurrence and aggravation of asthma developed after arrival in tropical areas was especially striking; similarly, primary attacks appeared quickly but less so than the former. The cause or causes of this phenomenon, not previously reported on, was not clear; however, the rapidity with which asthmatic symptoms developed suggested an allergic mechanism; recurrence representing the immediate reaction in the sensitized, and the primary attack the development of hypersensitivity in the non-sensitized person, or in those with latent tissue hypersensitivity.

The procedure of correlating in each patient the presence of allergy in the personal and family history with skin sensitivity as determined by skin reactions to pollens and inhalant dusts indicated that a state of hypersensitivity previously manifest or not was present in a great majority of cases. The further question of the immediate direct cause or causes, however, was not always clear. Symptoms of hay fever accompanied recurrence and primary attacks in about 50% of cases, suggesting that pollen was of probable significance. As recurrence and onset were non-seasonal, and atmospheric pollen in the tropics and the Australian areas concerned is perennial, it was con-

cluded that 110, or 52% of the cases, were primarily due to pollen and/or inhalant dusts. In addition 29 or 14% were considered as due to infections of the respiratory tract. Other tropical conditions of a physical nature, such as damp humid weather, temperature variations (from warm to cold) and physical and emotional strain undoubtedly aggravated, or even induced attacks in the susceptible individual. Damp humid weather and changes in temperature were quoted as the two most aggravating conditions encountered in the tropics. Here the days are hot and humid but the nights relatively cool and damp; and this is when symptoms were usually aggravated, or a non-productive cough began, soon followed by wheezing.

Chronicity and severity of symptoms necessitated the evacuation to the United States of 172 or 82% of this series. Of 126 patients—more than 50% of the series—who developed asthma in the United States, either prior to or after entry into service, 98 or 78% were returned to the United States. In view of this fact, it is doubtful whether any individual with clinically demonstrable asthma or a history of such should be sent to an overseas theater, unless limited service is directed. In any event, he should not be sent to tropical areas. Even the history of hay fever should be seriously considered as disqualifying for service overseas, unless, limited or restricted service is intended. In this respect War Department Regulations are clear. Paragraph 58f, MR 1–9, Mobilization Regulations on Standards for Physical Examination, dated 15 October 1942, states that "bronchial asthma is a disqualifying defect for military service." Physical Standards for Overseas Assignments of Officers, paragraph 1c (3), War Department Circular No. 102, dated 11 March 1944, lists as a disqualifying defect "asthma which has been incapacitating at any time during military service." War Department Circular No. 164, dated 26 April 1944, does not specifically refer to asthma as a disqualifying defect for overseas service for enlisted men, but paragraph 2, War Department Circular No. 316, dated 29 July 1944, amends paragraph 4, War Department Circular No. 164 by adding subparagraph a (6) as follows: "defects below the standard for induction as provided in MR 1–9, when in the opinion of the medical authorities concerned the defect is progressive in nature and/or subject to the development of incapacitating complications." The present study

demonstrates that even mild asthma, not progressive in nature, and not subject to the development of incapacitating complications in the United States, almost always has become aggravated, at least in this series, to the extent that duty, either general or limited, is possible in only a small number. More accurate questioning and greater appreciation of the significance of mild asthma or the history thereof in the prospective soldier should have prevented the dispatch overseas of over half of the patients in this series. It is encouraging to note that a comprehensive program for study and treatment of allergic disturbances in the army has been started in the United States (2). A selected group of patients in this series was treated by desensitization. The efficacy of such therapy is difficult to measure, as the number of patients so treated is small; however, it was possible to retain by such treatment only a small number of patients for service in this theater.

Summary: 352 cases of asthma representing 1.2% of total admissions were observed at a General Hospital in the Southwest Pacific Area.

Of these, 209 were studied in detail, and an analysis thereof is presented. 107 developed asthma prior to service; 102 after entering military service. 136 were inducted, 51 enlisted, 13 entered through the National Guard, and 8 were officers. 109 were admitted from other hospitals, 98 from Base or unit dispensaries, and 2 were not admitted but were studied in the out-patient department.

119 of 130 patients serving in the tropics experienced prompt aggravation or recurrence of symptoms; only 11 were not made worse. 66 patients developed their primary attack in the tropics. The rapidity with which aggravation or recurrence developed after arrival in the tropics was most striking; likewise, the primary attack appeared quickly but less so than the former. This sequence suggested an allergic mechanism.

Development of asthma, either recurrence, aggravation or primary attack, was perennial; seasonal factors apparently exerted no influence thereon. Atmospheric pollen in the tropics, and in Australian areas concerned can be found throughout the year.

A positive family or personal history of hay fever and/or asthma and of skin sensitivity to pollen and other inhalant antigens was found

singly or in combination in the majority of patients. Conditions which aggravated or induced attacks in the susceptible individual were multiple; in addition to pollen and other environmental dusts, damp humid weather, diurnal temperature variations (from warm to cold) and physical and emotional strain were involved.

After consideration of all the data, 115 or 55% of the cases were considered as due to pollen and inhalant dusts; 29 or 14% to infection, and in 65 probable causes could not be defined. In these, however, environmental conditions probably played an important part.

The disability rate per patient represented only by hospital days in this theater was rather high: the minimum was 5, the maximum 225, and the average 58.98.

172 patients, or 82% of the entire series, were evacuated to the United States as unfit for duty in this area. 98 or 78% of the 126 patients in whom asthma developed in the United States, either prior to or after entering service, were returned to the United States.

Specific treatment, namely, desensitization to the indicated pollens and other environmental dusts, was instituted. No conclusions concerning the efficacy of such therapy could be reached; in a small number of cases, such treatment appeared to be beneficial and abled the patient to remain on duty.

On the basis of this study, it is suggested that any soldier with a history of or manifesting mild asthma should not be sent to an overseas theater, unless limited or restricted service is understood. In any event such indivuals should not undertake tropical service. Even the presence of hay fever should be seriously considered as a disqualifying condition for general service overseas. Army Regulations—MR 1–9, dated 15 October 1942—state that bronchial asthma is disqualifying for military service. If this regulation were strictly adhered to, fewer cases of asthma would be overseas.

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THE CLINICAL TEACHING OF SOCIAL MEDICINE[1]

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Richard Cabot found his inspiration for medical social service in Alice in Wonderland. My interest in social medicine has been stimulated largely by association with Ida Cannon.

I had not the pleasure of personal acquaintance with Miss Brogden, but I am told she was in many ways like Miss Cannon, and that means she was a noble person. One of the traits, I am told, which Miss Brogden had was a keen understanding of what sickness means to the individual. I can assure you that it gives me deep satisfaction and pleasure that you have done me the honor of asking me to give the first Brogden lecture in her memory. I pray that I may prove adequate. For my subject I have chosen that part of the general area for which the memorial is established, in which I have had some personal experience, namely, the teaching of social medicine to medical students at the bedside.

In these days of cataclysmic human events it is not necessary to dwell on the meaning of the word "social" beyond reminding you that it is derived from the Latin socius a companion, nor to stress the fact that not alone in medicine but in nearly any scientific discipline, social factors should be integrated with the biological or physicochemical. Indeed even the pure physicist will do well to consider the human inpacts of his purely physical discovery. That devotees of the natural and exact sciences are becoming aware of this need is made manifest among other things by the fact that last winter in three numbers of Science the leading article had to do with social sciences and their implications.

I will start the discussion of my subject with a brief consideration of the motivations and functions of the physician. Why do men and women elect to go into medicine? What do they expect to accomplish when they get there?

[1] First Brogden Lecture, delivered at Johns Hopkins Hospital, October 22, 1945.

For many years I have asked medical students and recent graduates in medicine competing in the intern examinations, why they chose medicine. Jacques Barzun (1), in his scintillating book "Teacher in America" indicates that this is a foolish question. Nevertheless I have asked it and received many replies which at least were interesting. I have not attempted to subject them to statistical analysis, but I can say with some confidence of being accurate, that more than half replied that they were drawn to medicine because they like people and want to help them. A considerable number were inspired by the example of a family doctor, a medical father or brother, or some other vivid human example. A much smaller group claimed as their motivation, genuine scientific interest and a desire to add to medical knowledge. A few very honest souls admitted that medicine attracted them because it seemed a relatively secure and pleasant way to earn a living, and because the doctor holds an honorable position in society.

These replies bring out, at least, that men and women enter the profession of medicine with a variety of motivations, which is as it should be, and also they point to the fundamental dichotomy of medicine, namely, the biologic versus the social, the unification of which is one of the objectives of medical education.

To the responsibilities and functions of the physician I have given much thought. It behooves those of us who try to teach these things to think about them occasionally. For many years I have given to each new group of medical ward clerks what my secretary has been pleased to call a fight talk. The points chiefly stressed on this occasion are that the student is going to have to shoulder some responsibility for the care of the patient, and that this is to the student's advantage (and we hope the patient's also), because responsibility is a great teacher. The student is actually about to begin the practice of medicine by playing a responsible part on a professional team which has to care for patients assigned to it. He is asked to read Francis W. Peabody's (2) lecture on the "Care of the Patient" in which the plight of the sufferer newly arrived in the possibly terrifying atmosphere of a hospital ward is portrayed with beautiful understanding, and Lawrence J. Henderson's (3) lecture entitled "Doctor and Patient as a Social System" in which it is made clear in the sparkling prose of that philosopher, that expressed or enacted sentiments of doctor or patient each affect the other, in a fashion analo-

gous to the impact of components in the physico-chemical system of Willard Gibbs. The doctor must develop enough insight into his own personality so that the impact of his behavior will work benefit, not harm, to the patient as they develop their rapport. The student is asked to remember all this as he sits down to take a patient's history. He is, in this first interview, initiating the vitally important doctor-patient relationship, not merely extracting information for the record.

At this point also we try to identify our objectives, that is to say, the function of the physician. One approach makes it clear that it is his function to make (or try to make) a diagnosis, to the end that he may plan and carry out rational treatment; also that for various self-evident reasons, a prognosis should be attempted. My friend since student days, Carl Binger (4), has lately written brilliantly on "The Doctor's Job." The doctor's duty toward his patient could hardly be better stated than in Binger's book. Also he makes it abundantly clear that the doctor has a responsibility in public medicine as well as private, toward the community, as well as to the individual patient. My chief criticism of Binger is that I fail to find in his work any adequate positive statement about the doctor's duty to teach, and to investigate the nature of disease. These omissions struck me rather forcibly because I have long felt that the physician has a threefold function—to care for the patient, to pass on his skill, and to search for the causes of disease, and discern methods for its prevention and cure.

The duty of the doctor to his patient is self-evident. This duty is common to all practitioners of medicine regardless of the conditions under which they practice. The obligation to teach and conduct research is is less evident and needs some scrutiny. On the fly-leaf of his book Binger reproduces the oath of Hippocrates. In this we find the words, "To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physician's oath, but to nobody else."

While formal teaching and research in medicine have now become to a considerable degree special callings within the over-all profession of

medicine, the Hippocratic oath certainly implies that any doctor should teach when called upon to do so. And I firmly believe this needs emphasis. Nothing is so salutary to one's own skill as trying to impart it to others. I always liked the title of Bliss Perry's book, which he got from Chaucer, "And Gladly Teach." Every doctor of medicine should teach whenever he gets the opportunity, not alone to help others, but to help himself, and if he does he will find deep satisfaction in it.

Finally I would like to submit that it is the privilege of any doctor of medicine to add at least some crumb of new knowledge as he goes about his work with his eyes open and his wits active. Research is the life blood of scientific progress, and while there are those who will devote a major portion of their time to organized investigative work, it should not be thought that it is their exclusive privilege to engage in such activities. The many also can do their bit if they have sufficient desire, curiosity, and imagination. It is healthy to inculcate on students that always to be seeking the cause of phenomena observed makes medicine more exciting and satisfying. Curiosity is of fundamental importance. Those who lack it innately should seek to cultivate it. It was because he was so curious about what people eat, or neglect to eat, that George Minot discovered the cure of pernicious anemia. It was because he was curious about the cause of a chance happening that Flemming discovered penicillin.

And now let us gather by the bedside. The bedside in question is in the public ward of a teaching hospital. A patient entered yesterday afternoon. A clinical clerk took his history. That is to say, he established professional contact with the patient in behalf of the whole professional team. The clerk has also made a physical examination; so has the intern; both have been checked by the resident. Now the whole is lined up, headed by the senior staff physician to mobilize its forces, to study the situation carefully, and decide what treatment is needed.

Is such a visitation an ordeal for the patient? It can, but if rightly managed, need not be. Indeed oftentimes it is a satisfaction to him. Most people like attention, and the patient in question is certainly getting it, or at least his disease is. The staff physician in charge must take the lead in putting the patient at ease. A few kindly words of explanation of what the occasion is about usually serves this purpose.

Then, too, in relating the history the clerk should be considerate and use such language and emphasis as he would want used about himself if he were to change places with the patient. The kind of jargon sometimes used like, "The patient is a well developed and nourished colored female para five, etc." is stupid and discourteous. For statistical purposes the facts must be recorded, but they shouldn't be recited in such a stereotyped rigmarole within the patient's hearing.

A good principle for the doctor, said the late Professor L. J. Henderson, is "do as little harm with words as possible". It is hard at times to practice what one preaches. I had been preaching this Hendersonian gospel when not long ago one of my interns informed me that I had said before a patient in clinic, that she had classic Graves' disease. The patient thought, said he, that this was a prognosis, and referred to the grave!

One very effective way on rounds of establishing a good rapport is to show an interest in where patients come from, French Canada, Scotland, Texas, Italy, or what. If the doctor has been to the locality himself and can recall some item familiar to the patient, it forms a useful bond at once. It seems to strengthen the patient's belief that he is among friends; that he will be treated with understanding. This is particularly important in a country as conglomerate as ours.

Having heard the story and examined the patient, the team, which includes not only staff doctors and medical students, but the head nurse and ward social worker, if possible, as well as professional guests from any quarter of the earth, then goes into a huddle, out of the patient's earshot, preferably outside the ward. Under the leadership of the senior physician all present should take part in putting together the clinical picture, much as a group of people might put together a jigsaw puzzle.

A diagnosis or interpretation of the picture should be attempted, based on all the pertinent evidence that is forthcoming from any of the group. It is at this point that the social factor may come into high relief. The student has gathered some elementary social facts in taking his history, but he has got them only by hearsay.

The picture of illness is the resultant of the impact of all harmful or mischievous forces which impinge upon the patient from without, and of his innate or acquired reaction pattern from within. In the etiology of disease the entry of bacteria into his body may be no more important

than marital unhappiness or fear of want. There are cases in which the biologic part of the picture is the more important part. Cure the pneumonia of the previously healthy, well adjusted person, and no social problem of consequence remains (except perhaps how to pay the bill?). In other cases the biologic factor is trivial and the etiology is mostly in the bad social set-up. To reconstruct the whole clinical picture it is necessary to know something of the patient's personality and environment, as well as of his biologic reactions to noxious agents which have impinged upon or gained entry to his body.

The patient in a hospital is an uprooted organism. He comes from, and has to go back to, an environment which in the case of all chronic diseases, and in many acute ones, is an essential part of the total clinical picture, background perhaps, but backgrounds are as much a part of pictures as foregrounds. Lacking either the picture is incomplete.

The evidence then upon which a truly complete diagnosis must rest may be biologic, psychologic, or social. Often it is all three. The physician of an earlier time had to gather all of it for himself. Before the days of clinical teaching in hospitals he had to teach medical students by the apprentice system to boot. There was old Dr. Holyoke (6) of Salem who practiced for seventy-five years or so in the eighteenth century, who not only did a huge practice, but was veritably a one-man medical school as well, in that he trained during his long professional life—he lived a full century—no less than thirty-five medical apprentices. In caring for his patient he either dealt with social problems by some contrivance of common sense, or they dealt with themselves. In his day if people were unhappily married they just took it, or found some solution other than divorce.

But nowadays these tasks must be divided to some extent. The team has taken the place of the individual physician. The social worker has become indispensable, particularly in relation to hospital medicine, but to an increasing extent in private practice also.

The physicians, with or without the aid of consultants, may make a fair shift to collect and interpret the biologic data, but in the hospital milieu the social worker, who sees the troubled, overanxious patient, or his family group, and can relate herself to his home situation and responsibilities with skill in discerning what social factors influ-

ence his illness, is indispensable to the making of an accurate, complete diagnosis. Hers is as Miss Cannon puts it, the social laboratory. The data it yields may equal or exceed in importance those of the several medical laboratories or of the physical examination of the patient. Even in outside practice when the doctor visits the home and observes the environmental situation, he may not adequately evaluate or deal with it, because it may require a social skill beyond him. To make him aware of his needs and limitations in this regard should be an objective in the training of the practitioner of medicine. In making diagnoses it is essential to think of all the possibilities. If we don't think of them we may miss the diagnosis. This applies to social as well as to biological factors.

The kind of evidence that the social worker may gather is very varied. To a considerable extent it has to do with resources and nature of the patient's human contacts—all the difficulties of the home, the causes of maladjustments, spouses, children, food, money. Also it, has to do with occupation, work, play or the lack thereof. I recall three cases of scurvy in elderly bachelors. Scurvy is due to lack of vitamin C. Yes, but why did these old codgers lack vitamin C? The investigation of their home—or more exactly, domiciliary—situation disclosed the over-all fact that the elderly male living alone is a very poor provider. Elderly women get along alone rather well on the whole, but the lonely human male is rather helpless. He lacks the something or other that is required to provide for so elemental a need as an adequate diet. In southern poor white areas this seems to be true of both sexes, although negroes living in the same type of environment get on comparatively well.

The complete diagnosis must be an epitome of all elements that enter into the clinical picture, social as well as biologic. It must include not only the disease, but an understanding of the patient who has it. A diagnosis of scurvy alone is not enough. It is necessary to know also how and why the patient received a diet which produced scurvy.

In brief, diagnosis is not merely an answer to what has the patient got, but how did he get it and why? as well. Without his social data the latter often cannot be answered at all.

When a diagnosis has been achieved, then treatment must be planned

and carried out. In the type of practice I am describing this is begun in the hospital ward, or OPD but always there should be vividly in mind to what the patient will go upon discharge. Here is where the student, if his interest has been aroused, can learn a lot about social medicine. He will see his patient daily and by successive interviews and by conversations with his relatives and friends increase his understanding of the background. During this time the medical members of the team should cooperate closely with the social worker, except in those cases in which the patient has good control of his social situation. During this period of study and care of the patient in hospital by a professional team, it is very important to the patient's peace of mind that the team present a united front with respect to what is said to him. If different doctors, nurses, or social workers tell him different things about his case, it destroys his morale.

While the doctors are attending to the more strictly biologic aspects of a case, the social worker will be evaluating its social hazards, not only from the patient's own viewpoint, but of the mischief his illness may be working upon his family. Patients may be so overwhelmed by social problems which they cannot solve that it may be impossible to treat them successfully until these problems are solved. Miss Dorothy E. Kellogg, our chief medical service social worker, has defined the function of her calling with respect to treatment as being to enable the medical care which the doctor thinks necessary, actually to be carried out.

My own special interest within the general field of medicine is the thyroid gland and its disorders. The social worker attached to our Thyroid Clinic has unearthed from time to time social items that dovetail in with the strictly endocrine in an amazing manner. Some marital difficulties turn out to be simply related to disturbances of thyroid function. Indeed I have meant for some time to write of these under the title, "Cupid and Thyroid". The personality changes which myxedema produced in one wife, for example, caused her husband to take to drink. When she had been restored to health, and the nature of the situation explained to him, he ceased drinking. In the case of another wife with myxedema, the husband said she had become so placid that it gave him the jitters. He spoke truly indeed, for he had developed Graves' disease. They both were restored to

health—the one by thyroid, the other by thyroidectomy, and I hope are living happily ever after.

The impact of war which is a social hazard of first magnitude, has produced all manner of pictures of illness, not only among those who serve, but among those who stay at home and suffer the consequences of separation, anxiety, and unaccustomed toil. Very frequently we have seen women develop thyrotoxicosis when a husband or son went overseas, or were reported wounded or missing.

The exposure of the student to such problems in the clinic and particularly letting him take a responsible part in actual case work, is the chief instrument by which he learns clinical medicine: the actual application to the care of the patient of the theory he has learned. I have always liked the title of our oldest chair of medicine, "The Hersey Professor of the Theory and Practice of Physic". If by physic we mean all methods of treating illness short of surgery, we have here a very sound and comprehensive description of the function of the clinical teacher.

The question of whether ward clerks should attend regular ward rounds, or have special purely teaching rounds arranged for them is important. My own belief is that it is very desirable that clerks go on regular rounds. The advantages of this are several. For one thing it makes them feel they are part of the team, that they are spending their time on something directly contributory to the patient's welfare, instead of talking part in a purely educational exercise of no obvious benefit to the patient. That their work actually counts in the patient's care is a great stimulus to them. Segregation in special teaching rounds can have the opposite effect. The atmosphere of the regular ward round can be one in which all concerned can learn. Each member teaches, and can learn from, every other. Visiting physicians are constantly kept up to date by their house staffs. Interns acquire valuable information from students. We even hope that students occasionally pick up something of practical wisdom from their elders. The situation, as Walter Cannon (7) has quoted William James, has the fecundity of aggregation, which is another way of saying it is valuable to put heads together.

This brings up the effect of the teaching atmosphere on the patient, and, because it is similar, that of research. One often hears the lay-

man say, "I don't want my wife made a human guinea pig." "I don't want my sister exposed to medical students." Now the facts are that both teaching and research improve the quality of the care given the patient, and that if the chief of service is doing his job adequately, neither one will work any injury. The important thing is to explain fully to patients what it is all about, and obtain their active cooperation. Taking part in education or investigation gives the patient a feeling that he is contributing to human progress, and in a great majority of cases this is gratifying to him. It makes his stay in hospital seem less of a dead loss than it otherwise would be.

The quality of care is improved by teaching and research, because diagnoses are on the whole bound to be more accurate when every observation is checked, every opinion exposed to criticism. If the right spirit prevails in the group, consideration of patients' feelings can be as sensitive in the ward as in the isolated room in the private pavilion, and the chances of right diagnosis and correct treatment are greater. The teacher must learn how to fulfill simultaneously his duty toward his patient and his duty toward his student. If he is mindful of this dichotomy he can master it.

I don't wish to imply that regular ward rounds are all that is needed in the instruction of ward clerks. They should be supplemented, of course, by various other types of session, case exercises with an instructor, occasional seminars and conferences. Of particular note for our present purpose is the medico-social conference, and on how we have conducted these for a number of years I would now like to speak.

In the "fight talk" at the beginning of the medical clerkship, to which I have already referred, the students are asked to pick out from among the cases assigned to them, one in which they would like to study the social factors unusually intensively. They are given in the form of a written outline, directions on how to proceed, through the patient himself and through his relatives and friends, with the social study of such a case. Having followed these the student writes a special medico-social case report and brings it to the conference, held every four weeks, when he presents it to the group, which includes a medical instructor, a social worker, and his fellow students. The objective in each case is to bring out clearly the medical indications for treatment, and then determine in discussion, how the social hazards

impeding it can be overcome. Over a period of fourteen years we have amassed about 650 students' medico-social case reports, and they constitute a highly informative collection of data, on a wide range of social difficulties that concern the patient, the physician, and the community.

Still another type of medico-social conference has developed among us as a result of the changes in internships and residencies forced on us by the war. Once a week the teams of each of the wards, namely, the resident, interns, ward clerks, head nurse and social worker, get together informally and review the treatment of all their patients, particularly with the object of making a well integrated plan for follow-up after discharge. The clerks summarize their cases, and then the others add any pertinent data acquired by their special skills. These exercises have made for better care of the patient, and all taking part in them have improved their grasp of the total case problem.

A little earlier I expressed the view that in selecting a medical career more young people seem moved by its human interest than by its scientific. As students proceed through medical school, however, they seem to become more and more absorbed by the biologic aspects of their subject. They become more interested in diseases than in patients. But undoubtedly, sound medical practice demands that they be interested in both.

Selection not only of students but of teachers is important in this regard. Do we pick students with a view to their interest in social sciences, or professors either for that matter? Probably not very often, although now as at Oxford, or Long Island, one sees occasionally the establishment of chairs of social medicine (8). But if the teacher is to be inspiring in the field of social medicine, he must have more than an intellectual interest in it himself. Such interest can be cultivated even if it does not grow naturally. For example, I am at the present moment intensely interested in what role lipo-proteins play in the action of the thyroid hormone upon its end organs; also why fat swells the orbital contents in certain cases of Graves' disease. These are genuine and legitimate interests. If I were a biologist only they perhaps would be sufficient, but as a physician, I must also be interested in my patients' welfare. How is he to adjust to the disability which his eye condition imposes? I may have to cultivate

my interest in the latter problem, but this is not difficult. Furthermore, another physician may have a primary interest in the patient's personal problem. He then will have to cultivate his interest in the biologic aspects, for practice must rest on sound theory. But the point is that each of us must have both interests. Whichever one is not instinctive must be cultivated.

The medico-social conference has been effective in creating interest in social medicine chiefly, I think, by demonstrating to students and teachers alike, that social facts contribute to, and sometimes indeed make, the diagnosis, and that social hazards may thwart treatment. Social science, I believe, would be still more exciting to students if it could be made experimental. When we first started our medico-social conferences, students were often quite frankly bored. As the years have gone by their interest has steadily increased, and the quality of their case studies improved. This appears to be due to participation in discussions, committing themselves on important issues which have to be thought through, and some actual responsibility in the care of the patient in the social as well as in the biologic aspects of diagnosis and treatment, and to discovering how social medicine is after all an integral part of ordinary clinical medicine.

The type of clinical material that lends itself well to the social teaching objective includes patients with such chronic maladies as peptic ulcer, ulcerative colitis, arthritis, heart disease, cancer, and all manner of psychoneuroses where something can be done to improve the environment sufficiently as to make adjustment achievable. In most cases it should not be difficult to accomplish something in this direction, because all adjustment is relative. There are those, for example, who can adjust admirably to the conditions of peace who cannot tolerate those of war.

The possibility, through medico-social measures, of diminishing the wastage caused by chronic illness, the management of hypochondriasis and other nervous illnesses in early phases, the doctor's and social worker's responsibility to the community in these matters all can be made convincing to the student through carefully made and well discussed case studies.

The social implications of man's increasing life span can be made challenging to the student. The field of geriatrics is absorbing. When

man does not die of infection, starvation, trauma or cancer, he wears out, his weakest system giving way first. If this is a vital one, he dies a death due to degenerative disease. Medical science may ultimately make a one horse shay of him, no part weaker than any other part, so that he will live his hundred years and a day and then simply fold up. When that happens it will give the social scientists something to think about.

The quality of students, as well as what and how they are to be taught, is pertinent to our discussion. I was recently deeply impressed by a paper by Hull (9) of the General Electric Company on the selection of personnel for industrial research. He listed four essential qualities in the order of their importance, as follows: character, aptitude, attitude and knowledge. It seemed to me that these are also requisites of the good physician. The placing of character first is of extreme importance. It is a quality hard to evaluate by credentials and examinations. It is only by personal contact that the moral fibre of a man can be measured. This is something for admission committees to think about. Hull doesn't mean that brains are not required, but his point, with which I heartily agree, that for my profession, as for his, brains alone are not enough.

The aptitude that Hull speaks of is a result of innate mental equipment. One is born with it or one is not. All that the selection of students can do is to determine whether a given individual possesses it.

Character, which includes positive honesty and unselfishness, on the other hand, can be nurtured. Attitude can be trained. Knowledge can be acquired.

In the training of the physician the development of *maturity* is of vast importance, and I would define maturity for this purpose as the possession of insight, of a sense of proportion and of some practical wisdom based on experience. Nothing matures medical students more successfully than taking clinical responsibility. The sooner they get it the better. But it must be given them in graded doses. Plenty of time for the digestion of experience, for its enrichment by study, must be allowed at each stage of their development.

In the development of insight some instruction in psychology, some guidance in the exploration of one's own personality, are necessary. This training should be begun for any calling in school and continued

in college. It is especially necessary to the physician because of the great dependence of his patients on his own personality. The development of his insight can be aided by telling him to ask himself, "why do I act the way I do? If I were the patient, how would I want to be treated?" is a good question, but it is not enough. The good physician will ask himself, "If I were the patient and had his personality, how would I want to be treated?" We once had in the ward an old man from Cape Cod. Every day his wife called upon him, whereupon a terrific battle ensued. The kindly, but not sufficiently mature or understanding intern, decided it would be to the patient's best interest if he stopped the wife from calling. When this had been in effect for a couple of days the patient summoned the intern and said, "Young man, you mean well, but I have been married to that damn woman for forty years, and I have to see her!"

The doctor must have his own number if he is to get accurately that of his patient. "Physician heal thyself" we read in Holy Writ. We need adjustment ourselves if we are to help others become adjusted. Similarly, the teacher cannot teach unless he himself is enthusiastic about his subject.

As the life span of man increases the social problems that his illnesses produce will increase. Binger has well pointed out that the negative accomplishment of preventing or curing disease is not enough. There must also be the positive promotion of health. This latter concept is on the whole foreign to the physician of today. As Binger points out, when the patient is over his illness he is apt to become uninteresting to the doctor. Here also is a matter for clinical teachers to think and to do something about. The vital problems of convalescence Binger rightly points out, up to now have been largely neglected. In promoting health of individuals, however, the doctor should not become officious. Many people are naturally rugged and independent, and are capable of managing their own affairs, provided they are supplied with up-to-date information.

For the further development of the teaching of medical students in social medicine, I think more use of home visiting is important. This can very likely be done by using the extra manpower which will soon be provided by a deluge of medical veterans seeking additional clinical training.

I have always thought the department of obstetrics, by putting students to work delivering women of babies in their homes, gave as good practical training (inadvertently, of course,) in social medicine as any in the school. Other clinical departments should offer this type of experience, but with a more directly social motivation.

I shall now bring this rather rambling discourse to a close by reading you a passage from that delightful work of Dobie, "A Texan in England". (pages 18 and 19).

"As far as quality of mind is concerned," says Dobie, "—and quality of mind is something that all the theories of democracy in the world cannot equalize—there is no detectable difference between top American students and top British students. The average student at the one English University I have acquaintance with is, however, better trained mentally, has the fibers in his mind better developed, enjoys the act of thinking more and has more intellectual curiosity than the average American student. He is more civilized, just as the average member of Parliament is more civilized than the average Congressman, less given to the puerile in thought, speech and conduct. He demonstrates how the charm of youthfulness may be added to by dignity and mental maturity. He gives a richer meaning to Wordsworth's 'The child is father of the man.'"

This is food for thought for all American teachers. In medical school I believe much can be done to promote both growth of mind and character by exposing the student constantly to the whole clinical picture, which includes the social as well as the biologic, and by giving him as responsible a role as possible in the entire care of the patient.

For your kind attention I thank you.

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